

## REMARKS

Applicants respectfully request reconsideration of the present application.

### 1. Disposition of the Claims and Specification

Claims 1-2, 8, 15 and 28-30 are currently pending. Claims 1-2, 8, 15, 28 and 30 are currently under consideration. Claim 29 has been withdrawn. Claims 3-7, 9-14 and 16-27 are canceled.

Claims 1, 15 and 28 are amended. Support for the amendment to claim 1 may be found in the specification, for example, at page 1, lines 2-3 and at page 5, lines 5-9. Support for the amendments to claim 15 may be found in the specification, for example, at page 32, lines 3-5 and page 36, lines 29-31. Support for the amendment to claim 28 may be found in the specification at page 7, lines 1-8. Claim 28 has been further amended to correct a grammatical error. Support for newly added claim 30 may be found in the specification, for example, at page 31, line 27, page 32, lines 3-5, and page 36, lines 29-31.

Because the foregoing amendments do not introduce new matter, entry thereof by the Examiner is respectfully requested.

### 2. Lack of Unity

The examiner has indicated that claim 29 does not have unity of invention with the claims of the elected invention because 37 C.F.R. § 1.475 does not provide for the inclusion of multiple methods of use within the main invention. Accordingly, claim 29 has been withdrawn from further consideration as being drawn to a non-elected invention.

### 3. Claim Objections

Claim 28 is objected to as being grammatically incorrect. The examiner has suggested that the claim be amended to recite "and" at the end of part (a). Applicants have amended claim 28 accordingly and respectfully request withdrawal of the objection.

**4. Claim Rejections – 35 U.S.C. § 112, Second Paragraph**

Claims 15 and 28 are rejected under 35 U.S.C. § 112, second paragraph. The examiner alleges that one of skill in the art would not be able to determine the “effective amount” recited in claim 15 based on the disclosure. The examiner explains that the phrase “effective amount” is indefinite because “the claim fails to state the function which is to be achieved and more than one effect can be implied from the specification or the relevant art.” Office action at 3-4. The examiner also states that the method of claim 28 appears to be incomplete because “the active step of ‘detecting the presence of any agonist activity in said sample’ ... provides no indication that the compound is being screened for agonist activity of the polypeptide of claim 1.” Office Action at 4.

Applicants respectfully disagree with the examiner. With respect to claim 15, Applicants note that page 38, lines 32-34 of the specification explains that a “therapeutically effective dose refers to that amount of active ingredient, for example NuBP or fragments thereof, ... which ameliorates the symptom or condition.” However, to expedite prosecution, Applicants have amended claim 15 to recite “a composition comprising a polypeptide of claim 1 and a pharmaceutically acceptable excipient.” Support for the amendment to claim 15 may be found in the specification, for example, at page 32, lines 3-5 and page 36, lines 29-31.

With respect to claim 28, Applicants have amended the claim to clarify that the claimed method detects the presence of “agonist activity of the polypeptide of claim 1.” Support for the amendment to claim 28 may be found in the specification, for example, at page 7, lines 1-8. Applicants respectfully request reconsideration and withdrawal of the rejection to claims 15 and 28.

**5. Claim Rejections – 35 U.S.C. § 101**

Claims 1-2, 8, 15 and 28 are rejected under 35 U.S.C. § 101. Applicants previously argued that the specification discloses that the claimed polypeptide appears to play a role in reproductive, immune, neurological disorders and cell proliferative disorders, and that the

claimed polypeptide may therefore be used to treat or prevent various diseases disclosed in the specification.

The examiner indicates that these arguments were not found persuasive. The examiner alleges there is no indication as to “what role the polypeptide ‘appears to play’ in any ‘reproductive, immune, and neurological disorders, and cell proliferative disorders.’” Office Action at 5. The examiner further states that the list of diseases disclosed in the specification is “exhaustive and non-specific.” Office Action at 5. Finally, the examiner reasons that “the specification fails to reasonably correlate the biological activity – if any – of the claimed polypeptide to a disease condition. As such, one must determine those diseases – if any – that can be treated or prevented using the claimed polypeptide.” Office Action at 5.

Applicants respectfully disagree with the examiner and respectfully request reconsideration and withdrawal of the rejection.

***A. The Specification Describes the Claimed Protein as a Zinc Finger Transcription Factor Protein.***

The specification describes the protein encoded by SEQ ID NO: 19 as a transcriptional regulatory protein that functions as a transcription factor. *See* page 1, lines 16-18. Transcription factors often incorporate DNA-binding structural motifs, such as a zinc finger. *See* page 1, lines 29-31. Specifically, Table 2 of the specification describes the claimed protein as a “CH2-type zinc finger protein.” The specification further discloses that “mutations in transcription factors contribute to oncogenesis ... due to the role of transcription factors in the expression of genes involved in cell proliferation.” *See* page 2, lines 27-28.

***B. Post-Filing Publications Confirm the Biological Role the Claimed Protein Plays in Cell Proliferative Disorders***

Applicants respectfully disagree with the examiner’s assertion that there is no indication as to “what role the polypeptide ‘appears to play’ in any ... cell proliferative disorder.” Office Action at 5.

According to the results of the attached sequence alignment, performed with SEQ ID NO: 19 of the instant invention, the protein identified in the specification having an amino acid sequence corresponding to SEQ ID NO: 19 is 99% identical to SNAI1. *See* Alignment (Exhibit 1). The annotation of SNAI1 (Exhibit 2) and associated post-filing PubMed articles confirm that SNAI1 is zinc finger transcription factor that represses both E-cadherin expression and aromatase expression, each of which are implicated in cell proliferation.

Cano *et al.*, NAT. CELL BIOL. 2(2):76-83 (2000) (submitted herewith in the attached IDS) (“Cano”), explain that Snail (SNAI1) is a transcription factor that interacts with the E-pal element of a promoter of E-cadherin and causes “strong repress[ion] of E-cadherin transcription.” Cano at pages 76-77. E-cadherin is believed to be a tumor suppressor gene, loss of which “is considered to be a diagnostic of a poor clinical prognosis.” Cano at 76. According to Cano, overexpression of Snail “leads to a dramatic conversion towards a fibroblastic phenotype at the same time that E-cadherin expression is lost and invasive/migratory properties are acquired.” Cano at 77. Cano also teaches that snail “is expressed in E-cadherin-deficient murine and human carcinoma cell lines and tumors.” *Id.* Specifically, high levels of Snail and corresponding low or undetectable levels of E-cadherin have been detected in breast cancer cells, colon cancer cells and melanoma. *See* Cano at 80. Cano summarizes these results as providing “strong evidence that Snail is involved in the downregulation of E-cadherin transcription that occurs during the progression of malignant tumors.” Cano at 81.

Poser *et al.*, J. Biol. Chem. 276(27):24661-24666 (2001) (submitted herewith in the attached IDS) (“Poser”), also explain that E-cadherin is “assumed to act as a tumor suppressor negatively regulating several critical steps of invasion and metastasis.” Poser at 24661. Specifically, “[t]ransfection of E-cadherin DNA into invasive carcinoma cells led to significant reduction of their invasive capacity” and “activation of E-cadherin resulted in growth retardation of tumor cell lines.” *Id.* Poser confirms that “significant expression of Snail closely correlates with down-regulation of E-cadherin.” Poser at 24664.

Okubo *et al.*, CANCER RESEARCH 61:1338-1346 (2001) (submitted herewith in the attached IDS) (“Okubo”), teach that aromatase, which converts androgen to estrogen, is expressed in higher levels in breast cancer tissue than in normal breast tissue. *See* Okubo at 1338. Aromatase gene expression is directed through several promoters, including the I.3 promoter. *Id.* SnaH (SNAI1), a zinc-finger transcriptional factor protein, binds to the promoter I.3 region and reduces promoter I.3 activity in aromatase. *See* Okubo at 1338, 1342. Okubo demonstrates that SnaH is expressed in high levels in normal breast tissue, but at low levels in breast cancer tissue. *See* Okubo at 1338-1339. Okubo concludes that these results indicate that “a reduction of the expression of SnaH in breast cancer tissue further suggests a cancer-protective role for this protein in normal breast tissue.” *See* Okubo, abstract.

Applicants submit that Cano and Poser, as described above, demonstrate that overexpression of the claimed polypeptide of SEQ ID NO: 19 results in repression of E-cadherin and a subsequent increase in cell proliferation, specifically breast cancer, colon cancer and melanoma. Further, Okubo, as described above, indicates that overexpression of the claimed polypeptide of SEQ ID NO: 19 may cause a decrease in aromatase expression, thereby preventing breast cancer. Accordingly, Applicants have demonstrated the specific role the claimed polypeptide plays in several cell proliferative disorders. Applicants respectfully request reconsideration and withdrawal of the rejection.

***C. Post-Filing Publications Confirm the Biological Activity of the Claimed Protein is Correlated with Specific Diseases Such as Melanoma, Breast Cancer and Colon Cancer, and is Therefore Useful in the Treatment and/or Prevention of Such Diseases***

The specification describes the claimed protein and related sequences as being useful in the diagnosis, treatment, and prevention of cell proliferative disorders including cancer. *See* page 1, lines 2-4 and page 4, lines 24-27. As described above, Cano, Poser and Okubo demonstrate that the biological activity of the claimed protein is associated with specific cell proliferative disorders such as breast cancer, colon cancer and melanoma. The specification specifically states that the claimed protein may be used to treat or prevent a disorder associated with either decreased or increased expression of the claimed protein. *See* page 30,

lines 23-25 and page 32, lines 10-11. Further, the specification specifically states that such disorders include “a cell proliferative disorder such as ... cancers including ... melanoma ... and in particular, cancers of the ... breast [and] gastrointestinal tract.” *See* page 21, lines 27-32.

Applicants assert that they have shown an established correlation between the biological activity of the claimed protein, as described above, with specific diseases disclosed in the specification, including melanoma, breast cancer and colon cancer. As such, one would not need to “determine those diseases – if any – that can be treated or prevented using the claimed polypeptide.” Office Action at 5.

For all of the reasons asserted above, Applicants respectfully request reconsideration and withdrawal of the § 101 rejection and the corresponding enablement rejection under 35 U.S.C. § 112, first paragraph.

**6. Claim Rejections – 35 U.S.C. § 112, first paragraph – Written Description**

Claims 1, 8, 15 and 28 are rejected by the examiner under 35 U.S.C. § 112, first paragraph. The examiner alleges that the claimed genus encompasses widely variant species with respect to structure and function. The examiner believes that the disclosure of the single representative species of SEQ ID NO: 19 fails to represent the “genus of variants of SEQ ID NO: 19 as recited in parts (b) and (c) of claim 1, particularly in view of the lack of correlation between the structure and function of the species of the claimed genus.” Office Action at 8. In this regard, the examiner notes that the species encompassed by this genus “can have any function and any structure that is at least 90% identical to SEQ ID NO: 19.” Office Action at 8.

Applicants respectfully disagree with the examiner. With respect to the examiner’s contention that the claimed genus encompasses species with “any structure,” applicants note that Table 2 of the instant specification describes relevant structural features of the claimed protein. Specifically Table 2 describes: (1) potential phosphorylation sites (S11, S25, S76,

S82, S90, S92, S96, S119, and T229); and (2) signature sequences (F154-H176, C180-H202, F208-H230, and Y236-C259) of SEQ ID NO: 19.

To expedite prosecution, however, Applicants have amended claim 1, part (b) to state that the claimed 90% variants have “nucleic acid binding activity.” Support for the amendment to claim 1(b) may be found in the specification, for example, at page 1, lines 2-3. Applicants have also amended claim 1, part (c) to indicate that the claimed polypeptide fragments are “immunogenic fragments” of the polypeptide having the amino acid sequence of SEQ ID NO: 19. Support for the amendment to claim 1(c) may be found in the specification, for example, at page 5, lines 5-9. Applicants respectfully request reconsideration and withdrawal of the rejection.

**7. Claim Rejections – 35 U.S.C. § 112, first paragraph – Enablement**

Claims 1, 8, 15 and 28 are rejected by the examiner under 35 U.S.C. § 112, first paragraph. The examiner alleges the specification “fails to teach how to make variants of SEQ ID NO: 19 that maintain the same biological activity. For example, the specification, fails to provide guidance such as those amino acids of SEQ ID NO: 19 that are conserved and those that can be replaced without affecting biological activity.” Office Action at 10.

The examiner also asserts that “the state of the art at the time of the invention acknowledged the high level of unpredictability in altering the amino acid sequence of a polypeptide with an expectation of maintaining the desired biological activity.” Office Action at 11. The examiner reasons that even if the scope of claimed polypeptides were limited “to those that have nucleic acid binding activity,” there would still exist a high level of unpredictability in altering the peptide sequence as evidenced by Branden *et al.* and Witkowski *et al.* Office Action at 12.

Applicants respectfully disagree with the examiner. With respect to the examiner’s statement regarding the failure to teach how to make variants that maintain biological activity and the unpredictability in the art, Applicants note that Table 2 of the specification describes: (1) potential phosphorylation sites (S11, S25, S76, S82, S90, S92, S96, S119, and T229); and

(2) signature sequences (F154-H176, C180-H202, F208-H230, and Y236-C259) of SEQ ID NO: 19. As such, Applicants assert that one of skill in the art, from reading the specification and Table 2, would know how to create a polypeptide 90% identical to SEQ ID NO: 19, so that the resulting polypeptide retains the same biological activity of that of SEQ ID NO: 19. Specifically, one of skill in the art would know to maintain those domains of SEQ ID NO: 19 identified in Table 2.

With respect to the examiner's statements regarding Branden *et al.* and Witkowski *et al.*, Applicants note that, as described above, Table 2 of the specification would provide the necessary guidance for altering the polypeptide of SEQ ID NO: 19, while still allowing for an expectation of retaining the nucleic acid binding activity of SEQ ID NO: 19. Applicants also note that while Branden *et al.* and Witkowski *et al.* describe the effect a single amino acid substitution may have on a protein's function, neither article relates specifically to the variation of a nucleic acid binding protein, such as the claimed polypeptide. Specifically, Witkowski *et al.* describes the conversion of  $\beta$ -ketoacyl synthase to malonyl decarboxylase and Branden *et al.* describes protein function and protein engineering in only general terms. For all of the foregoing reasons, Applicants respectfully request reconsideration and withdrawal of the rejection.

## **8. Conclusion**

Applicants believe that the present application is in condition for allowance. Favorable reconsideration of the application as amended is respectfully requested.

The Examiner is invited to contact the undersigned by telephone if it is felt that a telephone interview would advance the prosecution of the present application.

The Commissioner is hereby authorized to charge any additional fees which may be required regarding this application under 37 C.F.R. §§ 1.16-1.17, or credit any overpayment, to Deposit Account No. 19-0741. Should no proper payment be enclosed herewith, as by a check being in the wrong amount, unsigned, post-dated, otherwise improper or informal or even entirely missing, the Commissioner is authorized to charge the unpaid amount to

Deposit Account No. 19-0741. If any extensions of time are needed for timely acceptance of papers submitted herewith, Applicants hereby petition for such extension under 37 C.F.R. §1.136 and authorizes payment of any such extensions fees to Deposit Account No. 19-0741.

Respectfully submitted,

Date 11/19/04

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